Guidance for Industry

Manufacture, Processing or Holding of Active Pharmaceutical Ingredients

DISCUSSION DRAFT -- NOT FOR IMPLEMENTATION

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

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[1] This guidance has been prepared by the Division of Manufacturing and Product Quality in the Center for Drug Evaluation and Research (CDER), in a joint effort with CDER's Office of Pharmaceutical Science, the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM), in cooperation with the Office of Regional Operations, at the Food and Drug Administration. Although this discussion draft guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, the final document will represent the agency's current thinking on active pharmaceutical ingredients. For additional copies of this guidance, contact the Drug Information Branch, Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 827-4573).

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Table of Contents

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I. Introduction

A. Purpose

1. Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) deems a drug to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of the Act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

2. The Act's definition of a drug, at Section 201(g)(1), includes any article or any component of an article, that is: (a) recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to them; (b) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and, (c) (other than food) intended to affect the structure or any function of the body of man or other animals. As defined below, FDA applies the terms "active pharmaceutical ingredients" (API) and "bulk pharmaceuticals" to what the Act addresses as "components of an article."

3. The purpose of this document is to provide guidance on FDA's expectations regarding current good manufacturing practice (CGMP) for the manufacture, processing, packing, or holding of active pharmaceutical ingredients (APIs) for human and veterinary use, and biologic APIs.

4. This document does not in any way affect the ability of the agency to establish specific requirements or standards regarding APIs within the context of new drug application reviews. Likewise, this document is not intended to address specific issues relating to filings of such applications.

B. Spectrum of CGMP Controls

1. The agency expects CGMP controls to be applied to all steps in the manufacturing process, beginning with starting materials. FDA expects such controls to include the validation of processes determined to impact the quality and purity of the final API or biologic API.

2. FDA recognizes that at certain early production stages applying stringent controls may not be feasible or necessary. The stringency of controls, such as the extent of written instructions, in-process controls, sampling, testing, monitoring and documentation, in active pharmaceutical ingredient production should increase as the process proceeds from early intermediate stages to final synthesis and purification stages. In this document, the agency will attempt to clarify its expectations regarding the stringency of controls at different processing steps.

C. Scope

1. The document applies to the manufacture of active pharmaceutical ingredients and biological active pharmaceutical ingredients, including intermediates. These substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the human body of man or other animals.

2. This document does not apply to medical gases, bulk-packaged drug products (final dosage forms) and manufacturing/control aspects specific to radiopharmaceuticals.

3. Because the agency considers sterile active pharmaceutical ingredients to be drug products, their production is subject to the current good manufacturing practice regulations, 21 Code of Federal Regulations (CFR) parts 210 and 211. However, because those regulations were not intended to address synthesis of APIs this guidance only applies to the very early synthesis stages of their production.

D. Definitions

1. The definitions and interpretations contained in section 201 of the Act apply to such terms when used throughout this document.

2. "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

3. “Active Pharmaceutical Ingredient” (API) means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Although the agency has used term “bulk drug substance” to describe these materials, FDA is aware that the term active pharmaceutical ingredient has international recognition. In light of this recognition, and for added clarity, the agency is using the term active pharmaceutical ingredient in lieu of bulk drug substance in this document.

4. "Agency" means the United States Food and Drug Administration.

5. "Batch" means a specific quantity of an intermediate or API intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture.

6. "Bulk Pharmaceuticals" (BPs) mean materials (both pharmacologically active and inactive) which are intended for use as a component of a drug or biological product. These include materials manufactured by processes such as: (1) chemical synthesis; (2) fermentation, (3) recombinant DNA or other biotechnology methods, (4) isolation/recovery from natural sources, or (5) any combination of these processes.

7. "Biological Active Pharmaceutical Ingredient" means a material originating from a biological manufacturing process intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or injury in man. The substance may be administered independently or as a component of a finished dosage form.

8. "Biological Product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man.

9. "Chemical Reaction" means a process that involves a chemical transformation of a starting material or intermediate to form a new compound (e.g., bond formation, oxidation, reduction).

10. "Critical Process Steps" means production steps that must be controlled to ensure that the intermediate or API will meet specifications for identity, strength, quality and purity.

11. "Drug Product" means a finished dosage form, for example, a tablet, capsule or solution, that contains a drug substance, generally, but not necessarily, in association with one or more inactive ingredients.

12. "Equipment Suitability" means establishing confidence that process equipment and ancillary systems can consistently operate within established limits and tolerances.

13. “Expiration date” means the date before which the API or intermediate meets all applicable specifications when stored under defined conditions, and beyond which these materials can no longer be used.

14. "Extraneous Substance" means an impurity arising from any source extraneous to the manufacturing process.

15. "Impurity" means any component of the API or the biological API (excluding water) which is not the material defined as the API or the biological API.

16. "Impurity Profile" means a description of the impurities present in a typical lot of an API or biological API produced by a given manufacturing process. The description includes the chemical identity, the range of each impurity observed, and the classification of each identified impurity.

17. "In-process material" is that which is in the state of being processed, e.g., the contents of a fermenting tank, a reaction vessel, etc. An intermediate is the product of in-process material.

18. "Intermediate" means a material produced during a manufacturing process that must undergo further molecular change or processing before it becomes an API or a biological API. Types of intermediates include:

    a. "Final Intermediate" means the last intermediate isolated and controlled during the manufacturing process, before the final step that creates the crude API.

    b. "In-Situ Intermediate" means an intermediate that is not isolated, however, requires adequate in-process controls before proceeding to the next step in the manufacturing process.

c. "Key Intermediate" means an intermediate in which at least one essential molecular characteristic, usually involving the proper stereochemical configuration required for structure or pharmacological/physiological activity, is first introduced into the molecular structure.

d. "Pivotal Intermediate" means an intermediate that may be prepared by more than one manufacturing process to provide material of suitable quality for use in the production of an API.

19. “Lot" means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits. For an API produced by continuous process, it is a specific identified amount produced in a unit of time in a way that ensures its having uniform character and quality within specified limits.

20. "Methods Validation" means the documented successful evaluation of an analytical method that provides a high level of assurance that the method will consistently yield reliable and accurate results, within previously established specifications.

21. "Mother Liquor" means a medium for synthesis containing unreacted starting materials, intermediates and impurities that may be reused for further processing, in the synthesis of an intermediate or API.

22. "New Chemical Entity" means a chemical that has not been adequately characterized in the literature regarding its physical and chemical properties.

23. "New Molecular Entity" means an API that has not previously been approved for marketing in the United States of America.

24. "Physical Manipulation" means a process that does not involve a chemical reaction that changes the purity or the physical properties of the material, including but not limited to, crystallization, gel filtration, chromatography, milling, or blending.

25. "Process Validation" means establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications

and quality characteristics.

26. "Purification Procedure" means a process, such as crystallization, distillation, or chromatography, intended to improve the purity of an intermediate, API, or biologic API.

27. “Range for Critical Process Parameter” means the range for each critical process parameter generally developed on research or pilot scale batches that encompasses values that are capable of producing intermediates and APIs with acceptable quality attributes.

28. “Reevaluation date” means the date prior to which an intermediate or API meets all applicable specifications, and beyond which the intermediate or API is not used without prior appropriate testing and examination.

29. "Reference Standard" means an API of high purity, specifically prepared by independent synthesis or by further purification of existing production material.

30. "Reprocessing" means introducing an intermediate or API that does not conform to established standards or specifications back into the process and repeating a step that is part of the validated manufacturing process (e.g., repeating a crystallization step using the same solvent).

31. "Reworking" means introducing an intermediate or API that does not conform to established standards or specifications back into the process and subjecting these to a step that is not part of the validated manufacturing process (e.g., repeating a crystallization step using a different solvent).

32. "Starting Material" means a commercially available component, obtained by commonly known procedures and well defined in chemical literature, used in the synthesis of an intermediate or API.

33. "Validation Protocol" means a written plan stating how validation will be conducted. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling and test data to be collected, number of validation runs, and acceptable test results.

34. "Working Standard" means an API or biological API of high quality and

purity, used as an analytical reference substance for routine laboratory analysis. The analytical testing needed to document the suitability of the working standard should generally be more extensive than that used for the API, and it is compared with a primary reference standard.

Note: Unless otherwise stated, when the following CGMP controls address APIs, the agency also intends to apply the same CGMP controls to biological APIs.

II. Organization and Personnel

A. Quality Control Unit

1. There should be a quality control unit that has the responsibility and authority to approve or reject all raw materials, intermediates, and APIs, and the authority to review production records to ensure that no errors or deviations have occurred and, if errors or deviations have occurred, that they have been fully investigated. The quality control unit should be responsible for approving or rejecting intermediates and APIs manufactured, processed, packed, or held under contract by another company. The quality control unit should be responsible for the review and approval of validation protocols and reports, and for the review of changes in product, process, equipment, or personnel to determine if revalidation is warranted.

2. Adequate laboratory facilities for the testing and approval (or rejection) of raw materials, intermediates, and active pharmaceutical ingredients should be available to the quality control unit.

3. The quality control unit should have the responsibility for approving or rejecting all procedures or specifications affecting the identity, strength, quality, and purity of intermediates and drug substances.

4. The responsibilities and procedures applicable to the quality control unit should be in writing and followed.

B. Personnel Qualifications

1. Each person engaged in the manufacture, processing, packing, holding or testing of an intermediate and active pharmaceutical ingredient should have the education, training, and experience or any combination thereof, to enable that person to perform the assigned functions. Training should extend to the

particular operations that the employee performs and current good manufacturing practice as they relate to the employee's functions. Training in current good manufacturing practice should be conducted by qualified individuals regularly and with sufficient frequency to ensure that employees remain familiar with CGMP controls applicable to them.

2. Each person responsible for supervising the manufacture, processing, packing, holding or testing of intermediates and active pharmaceutical ingredients should have the appropriate education, training, and experience to perform assigned functions in a way that provides assurance that APIs and intermediates have the safety, identity, strength, quality, and purity that they purport or are represented to possess.

3. There should be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, holding, or quality control of each active pharmaceutical ingredient.

C. Personnel Responsibilities

1. Personnel engaged in the manufacture, processing, packing, or holding of an API should wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand and arm coverings, should be worn as necessary to protect APIs and intermediates from contamination.

2. Personnel should practice good sanitation and health habits.

3. Only personnel authorized by supervisory personnel should enter those areas of the buildings and facilities designated as limited-access areas.

4. Any person shown anytime (either by medical examination or supervisory observation) to have an apparent illness or open lesion that may adversely affect the safety or quality of APIs should be excluded from direct contact with raw materials, intermediates, and APIs until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of APIs. All personnel should be instructed to report any health conditions that may affect active pharmaceutical ingredients to supervisory personnel.

D. Consultants

1. Consultants advising on the manufacture, processing, packing, or holding of

active pharmaceutical ingredients and intermediates should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

III. **Buildings and Facilities**

A. Design and Construction Features

1. Any building or buildings used in the manufacture, processing, packing, or holding of intermediates or active pharmaceutical ingredients should be of suitable design, size, construction and location to facilitate cleaning, maintenance, and proper operations.

2. Any such building should have adequate space for the orderly placement of equipment and materials to prevent mixups between different raw materials, intermediates, or APIs, and to prevent contamination or mixups. The flow of raw materials, intermediates, and APIs through the building or buildings should be designed to prevent contamination.

3. Operations should be performed within specifically defined areas of adequate size. There should be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the following procedures:

    a. Receipt, identification, storage, and withholding from use of raw materials or intermediates, pending the sampling, or examination by the quality control unit before release from manufacturing;

    b. Holding rejected raw materials, intermediates, and APIs before disposition;

    c. Storage of released raw materials, intermediates, and APIs;

    d. Manufacturing and processing operations;

    e. Packaging operations;

    f. Quarantine storage before release of intermediates and APIs;

g. Control and laboratory operations;

h. Where the specifications for the API include attaining high microbiological quality (as often happens for certain APIs intended to be incorporated into parenteral drug products) facilities should also be designed to exclude objectionable microbiological contaminants; and,

i. Operations relating to the manufacture, processing, and packing of penicillin, a substance that is potentially deleterious and difficult to contain, should be performed in facilities separated from those used for non-penicillin drug substances. Likewise, separate facilities should be used for cephalosporins and should be considered for other materials that are both difficult to contain and potentially hazardous.

B. Lighting

1. Adequate lighting should be provided in all areas.

C. Ventilation, Air Filtration, Air Heading and Cooling

1. Adequate ventilation should be provided.

2. Equipment for adequate control of air pressure, microorganisms, dust, humidity, and temperature should be provided when appropriate for the manufacture, processing, packing, or holding of intermediates and APIs.

3. Air filtration systems, including prefilters and particulate matter air filters, should be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures should be taken to control airborne contaminants. Production areas should be provided with adequate air filtration, exhaust systems or other systems to control airborne contamination.

D. Plumbing

1. Potable water should be supplied under continuous positive pressure in a

plumbing system free of defects that could contribute contamination to any API. Potable water should meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards should not be used in the potable water system.

2. Drains should be of adequate size and should be provided with an air break or suitable mechanical device to prevent back-siphonage.

3. Adequate washing facilities should be provided, including hot and cold water, soap or detergent, air dries or single-service towels, and clean toilet facilities easily accessible to working areas. There should also be shower facilities when needed, for example when dealing with hazardous materials.

E. Sewage and Refuse

1. Sewage, trash, and other refuse in and from the building and immediate premises is disposed of in a safe and sanitary manner.

F. Sanitation

1. Any buildings used in the manufacture, processing, packing, or holding of intermediates and APIs should be maintained in a clean and sanitary condition. Any such building should be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter should beheld and disposed of in a timely and sanitary manner.

2. There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities. Such written procedures should be followed.

3. There should be written procedures for use of suitable rodenticide, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures should be designed to prevent the contamination of equipment, raw materials packaging, or APIs and should be followed. Rodenticide, insecticides, and fungicides should not be used unless registered and applied according to the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

4. Sanitation procedures should apply to work performed by contractors or temporary employees and work performed by full-time employees during the ordinary course of operations.

G. Maintenance

1. Any buildings used in the manufacture, processing, packing, or holding of intermediates and drug active pharmaceutical ingredients should be properly maintained and repaired.

IV. **Equipment**

A. Equipment Design, Size, and Location

1. Equipment used in the manufacture, processing, packing, or holding of intermediates and APIs is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

B. Equipment Construction

1. Equipment should be constructed so that surfaces that contact raw materials, intermediates, or active pharmaceutical ingredients are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the intermediate and/or API beyond the official or other established specifications.

2. Any substances required for operation, such as lubricants or coolants, should not contact raw materials, intermediates, or APIs so as to alter the safety, identity, strength, quality, or purity of intermediates and APIs beyond the official or other established specifications.

3. Equipment should be designed, constructed, and installed to allow for ease of cleaning, and, as applicable, sterilization.

C. Equipment Cleaning and Maintenance Procedures

1. Written procedures should be established and followed for cleaning and

maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of intermediates and APIs. These procedures should include, but should not be limited to the following:

a. Assignment of responsibility for cleaning and maintaining equipment;

b. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

c. A complete description of the methods and materials used to clean and maintain equipment, including instructions for disassembling and reassembling each article of equipment to ensure proper cleaning and maintenance.

d. Removal or obliteration of previous batch identification;

e. Protection of clean equipment from contamination prior to use;

f. Inspection of equipment for cleanliness immediately before use.

g. Establishing the maximum times that may elapse between the completion of processing and equipment cleaning as well as between cleaning and equipment reuse.

D. Cleaning of Dedicated and Non-Dedicated Equipment

1. Regardless of whether or not equipment is dedicated to a particular active pharmaceutical ingredient, equipment should be cleaned between successive batches to prevent contamination and carry over of degraded material.

2. Where equipment is dedicated to production of successive batches of the same intermediate or API, equipment should be evaluated for cleanliness between successive batches to prevent carryover of contaminants or degraded material that can result from continually processing entrained residuals. As processing approaches the final purified API it is important to ensure that incidental carryover between batches does not adversely impact on the established impurity profile. However, this does not generally hold for biologic APIs where many of the processing steps are accomplished aseptically and where it is necessary to clean and sterilize equipment

between batches.

3. If equipment is used for different intermediates and APIs, proper cleaning from one batch to another becomes particularly important. If cleaning of a specific type of equipment is difficult, the equipment may need to be dedicated to a particular intermediate or API.

E. Equipment Cleaning Methods

1. Equipment, including utensils and storage vessels, should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the intermediate or API beyond the official or other established specifications.

2. The choice of cleaning methods, detergents, and levels of cleaning should be defined and justified. Selection of cleaning agents (e.g., solvents) should depend on:

    a. The cleaning agent's ability to remove residues of raw materials, intermediates, precursors, degradation products and isomers;

    b. Whether the cleaning agent leaves a residue itself;

    c. Compatibility with equipment construction materials;

F. Validation of Equipment Cleaning Methods

1. Cleaning methods should be validated. In order to successfully validate a cleaning method firms should have a thorough knowledge of the process, products produced, and equipment used.

2. Validation of cleaning methods should encompass worst case conditions.

3. The validation protocol clearly should describe the equipment to be cleaned, methods, materials and scope of cleaning, parameters to be monitored and controlled, acceptance criteria, location and size of samples, procedures for collecting samples, and analytical methods.

4. Validated analytical methods having specificity and sensitivity to detect

residuals or contaminants should be in place. The detection limit for each analytical method should be sufficiently lower than the acceptable level of the residue or the contaminant. The method's attainable recovery level should also be established because the quantity of a residue detected may not always represent the true amount present on equipment surfaces due to inherent limitations of the sampling technique and/or method of detection.

5. Residue limits should be practical, achievable, and verifiable and should encompass raw materials, intermediates, precursors, degradation products, isomers, and cleaning agents. Limits should be based on the composition/configuration of the equipment, characteristics of the substance being cleaned, and the next product in the production sequence. All cleaning methods should ensure that no visible residues remain after cleaning.

6. Practical methods of setting limits may include:

    a. Establishing a limit that is several orders of magnitude below the minimum known pharmacological or physiological activity level of the API or intermediate that is being cleaned from the equipment. This limit should be compared against the maximum amount of the residue found in samples, calculated by assuming uniform dispersion for the equipment. This amount of the residue should then be assumed to be transferred to the finished dosage product at its highest dosage level. The theoretical total amount of contamination should be calculated for one dosage unit and compared with the set limit.

    b. Establishing a limit based on successive cleaning and sampling until no further cleaning will lower the amount of the residue found on the equipment. It is important that the method of analysis to determine the residue be highly sensitive and that detection limits be considered in this approach.

7. With any limit, the hardest areas to clean on the equipment and the type of equipment surface to be cleaned, should be considered when sampling methods are developed. Methods should generally include swabbing and rinsing to detect both insoluble and soluble residues.

8. Cleaning/sanitization studies should address microbiological contamination

for APIs and intermediate processes for which microbiological contamination is a concern.

9. Cleaning procedures should be monitored by reduced sampling after validation to ensure that the these procedures are effective when used during routine production.

G. Clean in Place (CIP) Methods

1. It is important to carefully evaluate CIP systems. Although many can provide reliable cleaning, some systems may pose problems. For example, the configuration, size and placement of spray balls within a vessel to be cleaned are critical. Certain equipment designs make it difficult for cleaning solvents to reach all surfaces and crevices if the pressure/temperature of the cleaning spray is not well controlled. Material may also lodge in unused sampling ports or discharge valves.

2. For effective CIP systems, routine sampling may be less stringent than for manual systems based on traceable, controlled, process parameters.

3. Effective CIP methods reduce the need to disassemble equipment for cleaning purposes. Most CIP methods initially introduce water or pressurized steam into holding tanks, vessels, and transfer lines, followed by one or more washing steps with solvents or other chemical agents to dissolve remaining residues.

4. Although effective CIP cleaning methods may ensure more consistent and reliable results than manual cleaning procedures, these systems may be difficult to validate due to limited accessibility. Nonetheless, appropriate validation of CIP methods should be conducted.

H. Automatic, Mechanical, and Electronic Equipment

1. Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of intermediates and APIs. Such equipment should be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections should be maintained.

2. Appropriate controls should be exercised over computers or related systems to ensure that changes in master production and control records or other records are made only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data are checked for accuracy. A backup file of data entered into the computer or related system should be maintained, except where certain data, such as calculations performed in connection with laboratory analysis, is eliminated by computerization or other automated processes. In such instances, a written record of the program should be maintained along with data establishing proper performance. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to ensure that backup data are exact, complete, and secure from alteration, inadvertent erasures, or losses should be maintained.

V. **Control of Raw Materials**

A. General Controls

1. There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of raw materials. Such procedures should be followed.

2. Raw materials should be handled and stored in a manner to prevent contamination.

3. Bagged or boxed raw materials should be stored off the floor and suitably spaced to permit cleaning and inspection.

4. Each container or grouping of containers (lots) of raw materials should be identified with a distinctive code for each lot in each shipment received. This code should be used in recording the disposition of each lot. Each lot should be appropriately identified as to its status (i.e., quarantined, approved, or rejected). Weather-resistant labels should be used for containers of raw materials exposed to the weather.

5. Large storage containers, and their attendant manifolds, filling and discharge lines, should be appropriately identified as to status and contents.

B. Receipt and Storage of Untested Raw Materials

1. Upon receipt and before acceptance, each container or grouping of containers of raw materials, should be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

2. Raw materials should be stored under quarantine until they have been tested or examined and released.

    a. For hazardous or highly toxic raw materials, where on-site testing is not practical before off-loading of raw materials from transport containers to holding containers, suppliers' certificates of analysis should be obtained showing that the raw materials conform to specifications. Visual examination of containers, labels, and recording of lot numbers should also help in establishing the identity of hazardous or highly toxic raw materials. Justification for the lack of on-site testing should be documented for articles deemed hazardous.

    b. For raw materials that are not hazardous or highly toxic, at least one specific identity test should be performed. A supplier's certificate of analysis may be used in lieu of performing other testing. In such cases the manufacturer should have a vendor qualification program in place and should periodically verify tests performed by the vendor.

C. Use of Approved Raw Materials

1. Approved raw materials should be stored in controlled conditions, where appropriate, and rotated so that the oldest stock is used first.

2. Raw materials stored under conditions that may have adversely affected their quality should be periodically retested or reexamined, for strength, quality, and purity, and approved or rejected by the quality control unit. For example, raw materials may need such testing after prolonged storage or exposure to air or heat.

D. Rejected Raw Materials

1. Rejected raw materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations.

E. Control of Starting Materials, Reagents and Solvents Used In Production

1. Written procedures should be established to ensure that materials will maintain their identity, quality, and purity.

2. Written procedures should be established for the recovery of reagents or solvents, and include adequate tests and controls to ensure that the recovered materials are suitable for use in manufacturing processes. Fresh and recovered solvents and reagents may be commingled only after adequate testing has shown their suitability for all manufacturing processes in which they may be used.

F. Water Quality

1. Water used in the manufacture of intermediates and APIs should be demonstrated as suitable for its intended use and should not adversely alter the API quality.

2. Process water should be supplied under continuous positive pressure in a plumbing system free of defects that could contribute to the contamination of intermediates or APIs.

3. Water Used in Early Processing Steps

    a. Water for any API process should, at a minimum, meet the standards for potable water, as stated in the United States Environmental Protection Agency's (EPA) National Primary Drinking Water Regulations (NPRDWR) set forth in 40 Code of Federal Regulations, part 141.

    b. In addition to meeting EPA standards, potable water obtained from wells or surface sources should be assessed for pesticides, hazardous chemicals, and other contaminants that are not monitored by municipal water authorities.

4. Water Used in Final Isolation and Purification Stages

    a. During critical manufacturing steps, such as final crystallization and isolation of key intermediates and APIs, higher chemical and

microbial water quality specifications should be considered. For example, where the API needs to be of a high microbiological purity, appropriate action levels for total microbial count, objectionable organisms and endotoxins may need to be established and met. Higher specifications should also be considered during early manufacturing steps if impurities may affect the quality of the product or their removal cannot be validated in later steps.

b. Where water is treated to achieve an established quality, the treatment process should be validated and monitored to ensure that it consistently produces water of the desired quality. Piping systems that convey such water should be routinely monitored to ensure that water quality is maintained.

5. Where firms have made commitments to the agency (e.g., in new drug applications) regarding water quality, FDA expects those commitments to be met.

VI. **Production and Process Controls**

A. Written Procedures; Deviations

1. Written procedures should exist and should be followed for production and process controls, designed to ensure APIs or intermediates have the identity, strength, quality, and purity they purport or are represented to possess. These procedures, should be drafted, reviewed, and approved by the quality control unit and other appropriate organizational units.

2. Written production and process control procedures should be followed in the execution of the various production and process control functions and should be documented at the time of performance. Any deviation from the written procedures should be recorded and justified.

3. Written procedures should be established for scale-up of production or changes from established manufacturing procedures. These procedures should include appropriate provisions for validating the change process. Changes from established production and process control procedures should be approved by the quality control unit and other appropriate organizational units.

B. Charge In of Components

1. Written production and control procedures should include the following, which are designed to ensure that APIs and intermediates have the identity, strength, quality, and purity they purport or are represented to possess:

    a. Components such as starting materials, reagents and solvents for intermediate and API manufacturing should be weighed or measured as appropriate to maintain their identity, quality and purity. Measuring devices should be calibrated to ensure accurate results within appropriate ranges. If a substance is removed from the original container to another, the new container should be suitable and should be identified with the following information:

        (1) Material name and item code;
        (2) Receiving or control number;
        (3) Weight or measure of substance in the new container;
        (4) Batch or lot for which the component was dispensed, including the manufacturing sequence identification, production step, and reference to batch record and lot number.
        (5) Repackaging Date.

    b. Materials subdivided for use in production operations should be labeled (coded) in an appropriate manner so that the original batch of material can be identified. Subdivided materials should conform to the manufacturing/quality control specifications for the production of the intermediate or API.

    c. Verification, weighing, measuring, or subdividing operations for components should be adequately supervised. Each container of substance dispensed should be examined by a second person to ensure that:

        (1) The material was released by the quality control unit;
        (2) The weight or measure is correct as stated in the batch production records;
        (3) The containers are properly identified;
        (4) Substances for use in the production operation conform to the specifications for the intended manufacturing process.

C. Equipment Identification

1. All reactors, storage containers, processing lines, and other major equipment used during the production of a batch of an intermediate or API should be appropriately identified to show their contents and, when necessary, the manufacturing step for which they are intended to be used.

2. Major equipment should be identified by a unique identifier recorded in the batch production record to show the specific equipment used in the manufacture of each batch of an intermediate and API. Where only one piece of a particular type of equipment exists in the manufacturing facility, the name of the equipment may be used as the unique identifier.

D. In-Process Controls

1. To ensure batch uniformity and quality of intermediates and active pharmaceutical ingredients, written specifications and procedures should be established and followed that describe the in-process controls, tests or examinations to be conducted on in-process materials of each step in the process. Such procedures should be established to monitor the progress and control the performance of those manufacturing processes that may be responsible for causing variability in the quality characteristics of intermediates and active pharmaceutical ingredients. The specifications, type, and extent of testing should depend on several considerations, including:

    a. The nature of the intermediate or API being manufactured.

    b. The reaction or process step being conducted.

    c. The degree to which the step introduces variability in the process.

2. In-process controls for chemical reactions should include, as appropriate, the following:

    a. Reaction completion or time;
    b. Reaction appearance, clarity, completeness or pH of solutions;
    c. Reaction temperature;

d. Concentration of a reactant;

3. In-process controls for physical manipulations should include, as appropriate, the following:

a. Appearance and color;
b. Assay or purity;
c. Uniformity of the blend;
d. Temperature of a process;
e. Concentration of a solution;
f. Processing rate or time;
g. Particle size analysis;
h. Bulk/tap density;

4. In-process specifications should be derived from research or pilot scale batches or process variability estimates until sufficient process data is collected on full scale production batches.

5. All specifications and test results should be reviewed and approved by the quality control unit. Some tests may be performed by qualified production department personnel, and the process adjusted without prior quality control approval, provided adjustments are made within limits preestablished and approved by the quality control unit. All tests and results should be fully documented in the batch record.

6. Rejected intermediates and APIs should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

7. Testing and Control of Intermediates for Further Processing

a. Written procedures should be established and followed that describe the controls and tests to evaluate the suitability of pivotal, in-situ, and final intermediates intended for use in subsequent process steps.

b. The controls employed to ensure the suitability of intermediates should depend on the nature and stage of the chemical or biological reaction in which the intermediates are used. Less stringent control may be employed for intermediates used in early

processing steps, whereas tighter specifications and tests are used for key and final intermediates used in final synthesis steps.

c. Intermediates stored before further processing should be packaged and maintained in a way that ensures they remain suitable for use in the manufacturing process.

d. In-process blending of intermediate batches and incidental carryover should be adequately controlled to ensure the quality and the homogeneity of the final API. All intermediate batches to be blended should be tested and should meet all specifications prior to blending or mixing.

e. Rejected intermediates should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable. Materials identified for reprocessing should be quarantined until reprocessing operations are performed.

8. Time Limits on Production and Storage of Intermediates

a. When appropriate, time limits for the completion of each manufacturing step should be established to ensure the quality of intermediates and APIs. Deviations from established limits may be acceptable provided such deviations do not compromise the quality, purity or strength of the intermediate or API. Such deviations should be justified through adequate analytical testing and documented.

b. Written procedures for storage of intermediates should be established which include holding conditions, such as temperature, humidity, container/closure system and time limits. Storage time limits and conditions should be supported by adequate analytical or manufacturing data.

9. Calculation of Yield

a. Actual yields and percentages of theoretical yields should be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging or holding of an intermediate or API. Theoretical yields with appropriate ranges

should be established based on previous manufacturing data.

b. Deviations from established yield ranges often signal a problem in the process and should therefore be adequately investigated. Written control procedures should be established which describe corrective actions to be taken when yields deviate from theoretical values.

(1) Corrective actions should include: (1) determining releasability of affected lots, and (2) correcting manufacturing process or other sources of the problem in a manner to minimize the likelihood of problem recurrence.

10. Sampling of Bulk Materials

a. Written procedures should be established and followed that describe the sampling methods for all materials used in the manufacture of intermediates and APIs. Procedures should ensure that samples represent the batch or lot. Sampling plans for in-process materials, intermediates and APIs should be based on valid data and sampling practices.

b. Adequate control procedures should be established to ensure the quality, purity and integrity of samples after collection. Each sample should be labeled clearly to establish the identity of the material, and to show where the sample was obtained.

11. Control of Microbiological Contamination

a. For intermediates and APIs not required to be sterile, written procedures should be established and followed to prevent objectionable microbiological contamination, as appropriate.

b. For intermediates and APIs having specified endotoxin limits, written procedures should be established and followed to control endotoxin generation or contamination.

E. Blending Batches of APIs

1. Blending of finished batches of APIs should take into account the following

controls:

a. Each batch incorporated into the blend should be individually tested and found to meet all API specifications prior to blending.

b. Each batch incorporated into the blend should have been made from the same grades of similarly characterized raw materials, by the same facility, equipment and procedures.

c. The physical or chemical characteristics of each batch incorporated into the blend should have not been adversely affected by prolonged storage after manufacture. Appropriate limits on the maximum time allowable between production of individual batches and their blends should be established and followed.

d. The maximum lot size for the final blend should be limited to the maximum working capacity of the largest blender.

e. Any steps, such as drying, combined with the blending step should be performed in equipment designed to ensure blend uniformity.

f. The lot or control number assigned to the final blend should allow traceability back to the individual batches that make up the blend.

g. Blending processes should be validated to show homogeneity of the combined batch. Validation should include testing of critical product attributes that may be affected by the blending process. These attributes should include:

(1) Impurity levels;
(2) Moisture content;
(3) Particle size range;
(4) Bulk/tap density;
(5) Polymorphic form.

h. The quantity or size of individual samples taken from the blend should approximate the quantity required for purity and impurity assays.

2. Tailings (i.e., relatively small quantities of material not packaged with the

parent batches for reasons unrelated to quality) from different batches blended to form a single batch should come from previously tested and acceptable batches produced by the same process.

3. Stability testing of the final blended batches should be conducted, and should include:

    a. Assessing the storage containers for batches to be blended to ensure that they provide equivalent or better protection than the commercial container/closure for which stability data exists.

    b. Assigning the expiration date of the blended batch based on the manufacturing date of the oldest batch in the blend.

    c. Collecting stability samples from the final blend.

VII. **Packaging and Labeling Controls**

A. Materials Examination and Usage Criteria

1. There should be written procedures describing the receipt, identification, storage, handling, sampling, examination, and/or testing of API containers, closures, labeling and packaging materials. Such written procedures should be followed. Containers, closures, labeling and packaging materials should be representatively sampled, and examined or tested upon receipt and before use.

2. API containers, closures, labeling or packaging materials meeting appropriate written specifications should be approved and released for use. Any containers, closures or labeling that do not meet such specifications should be rejected to prevent their use in operations for which they are unsuitable.

3. Records should be maintained for each shipment received of API containers, closures and labeling showing receipt, examination or testing, and whether accepted or rejected.

4. Labeling for each different API strength, form or grade should be stored separately with suitable identification. Access to the storage areas should be limited to authorized personnel.

5. Obsolete and outdated labeling should be destroyed. Other obsolete packaging materials should be destroyed or otherwise disposed of in a way that precludes mixups with currently acceptable materials.

B. Packaging and Labeling Operations

1. To ensure that strict controls are exercised over active pharmaceutical ingredients labeling operations, there should be written procedures, describing in sufficient detail, controls for issuing and application of labeling. Such written procedures should be followed.

2. Labeling issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented in the batch production record.

3. Each API should be identified with a lot or control number that permits determination of the history of its manufacture and control.

4. There should be written procedures designed to ensure that correct packaging materials are used. Such procedures should be followed.

5. To prevent mixups and contamination there should be physical or spatial separations from other API operations.

6. Packaging and labeling facilities should be inspected immediately before use to ensure that all materials have been removed from previous operations. This examination should be documented in the batch production records.

7. After completion of packaging and labeling, API containers should be visually examined to provide assurance that all containers in the lot bear the correct labels. This examination should be documented in the batch production or control records.

C. API Containers and Closures

1. API containers and closures should not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the API beyond the official or established requirements.

2. Container closure systems should provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the API.

3. API containers and closures should be cleaned and, where indicated by the nature of the API, sanitized to ensure that they are suitable for their intended use.

4. Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sanitizing, and processing should be written and followed for API containers and closures.

D. Expiration or Reevaluation Dating

1. Antibiotic APIs are required by antibiotic regulations to bear expiration dates. All biological APIs should bear expiration dates.

2. Where data derived from stability studies demonstrate that a or API has limited shelf life when held under appropriate storage conditions, the labeling on the API should specify an appropriate expiration date.

3. Except antibiotic APIs, where data derived from ongoing stability studies show that an API is stable when held under appropriate storage conditions, a reevaluation date may be assigned in lieu of an expiration date.

4. Expiration or reevaluation dates should relate to any storage conditions stated on the labels, and should be supported by appropriate stability studies, as discussed below.

5. The supportable expiration dates or reevaluation dates along with related storage conditions should appear on the label of each container of finished lots of APIs.

6. Where applicable, labeled storage conditions should comply with standard definitions for "Freezer," "Cold," or "Controlled Room Temperature," as defined in the United States Pharmacopeia (USP). Statements of specific storage conditions should be used instead of more general terms such as “room temperature”. For most biotechnological and biological APIs, precisely defined storage temperatures are recommended. The label on each container should also bear any warnings, as appropriate, to protect the

contents from excessive heat, freezing, light or moisture.

VIII. Holding and Distribution of Intermediates and APIs

A. Warehousing Procedures

1. Written procedures describing the warehousing of APIs and intermediates should be established and followed. They should include:

    a. Storage under a quarantine system before release by the quality control unit.

    b. Storage under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the APIs and intermediates are not adversely affected.

B. Distribution Procedures

1. Written procedures should be established, and followed, describing the distribution of APIs and intermediates. They should include:

    a. A procedure by which the oldest approved stock of an API or intermediate is distributed first. Any deviations should be temporary and appropriate.

    b. A system by which the distribution of each lot of API or intermediate can be readily determined to facilitate its recall if necessary.

IX. Laboratory Controls

A. General Controls

1. Any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, should be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

2. Laboratory controls should be followed and documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms should be recorded and justified.

3. Laboratory controls should include the establishment of scientifically sound written specifications, standards, statistically valid sampling plans, and test procedures including resampling, retesting, and data interpretation procedures designed to ensure that starting materials, reagents, solvents, material containers, intermediates, in-process materials, and active pharmaceutical ingredients conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls should include:

    a. Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of starting materials, reagents, solvents, material containers, intermediates, in-process materials used in the manufacture, processing, packing, or holding of intermediates and APIs. Such procedures should also cover periodic retesting of any materials used in the manufacturing or holding of an intermediate or API that are subject to deterioration or degradation.

    b. Determination of conformance to written descriptions of sampling procedures and appropriate specifications for intermediates and APIs . Such samples should be uniform, representative, and properly identified.

    c. Calibration of instruments, apparatus, gauges, and recording devices at suitable intervals according to an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications should not be used.

B. Testing and Release for Distribution

1. For each lot of an intermediate and API, appropriate laboratory tests should be conducted to determine satisfactory conformance to final specifications, including the identity and strength of each material prior to release.

2. As appropriate, testing should be performed for organic volatile impurities and other major impurities.

3. Appropriate laboratory tests should be conducted on each lot of intermediate and API required to be free of objectionable microorganisms.

4. Sampling and testing plans should be described in written procedures that include sampling methods and quantities of samples to be tested. Such written procedures should be followed.

5. Acceptance criteria for the sampling and testing conducted by the quality control unit should be scientifically sound to ensure that lots of intermediates and APIs meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria should include appropriate acceptance levels and/or rejection levels.

6. The accuracy, sensitivity, linearity, specificity, and reproducibility, of test methods should be established and documented.

7. Intermediates and APIs failing to meet established standards or specifications and any other relevant quality control criteria should be rejected. Rejected materials may be reprocessed provided there are adequate written procedures in place and the reprocessed material meets appropriate standards, specifications, and any other relevant criteria.

C. Stability Testing[2]

1. There should be a written testing program designed to assess the stability characteristics of the API. The results of such stability testing should be used in determining appropriate storage conditions and expiration or

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[2]This guidance applies to stability testing for active pharmaceutical ingredients. FDA recommends that manufacturers also consult the agency's February 1987 "Guideline For Submitting Documentation For The Stability Of Human Drugs And Biologics," and the relevant International Conference On Harmonization (ICH) guidelines, including:

"Stability Testing of New Drug Substances and Products"
"Quality of Biotechnological Products: Stability Testing of Biotechnological /Biological Products"
"Light Stability Testing of New Drug Substances And Products"

reevaluation periods. The written program should be followed and include:

a. Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimate of stability;

b. Defined and controlled storage conditions specified on the label for the marketed product (e.g., temperature and humidity) for stability samples;

(1) Additional samples should be stored under stressful conditions (e.g., elevated temperatures, light, humidity and freezing) if such conditions can be reasonably anticipated.

c. Reliable, meaningful, and specific test methods;

(1) Testing should cover those features susceptible to change during storage and likely to influence quality, safety, and/or efficacy. Stability analysis should cover as necessary physical, chemical and microbiological characteristics. Validated stability-indicating test methods should be used.

d. Stability samples should be stored in containers-closures that simulate the market container. For example, where the API is marketed in polyliners within fiber drums, it is acceptable to package stability samples in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums. It also is acceptable to store the bags representing different batches/lots in a drum similar or identical to the drums actually used for marketing.

e. An adequate number of API lots should be tested, at suitable intervals, to determine an appropriate expiration or reevaluation date, and records should be maintained of such testing.

(1) Expiration or reevaluation dates and related storage conditions should be derived from long-term stability studies that include at least three batches in the testing program. However, where data from previous studies or from literature shows that the API is expected to remain stable for an extended period, (e.g., stable for at least two years), fewer than three batches may be used in the initial testing program.

(2) Pilot scale batches may be used if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale. If pilot scale batches are used to develop a tentative expiration date, the first three commercial production scale batches manufactured should be placed on long-term stability using the same stability protocol.

(3) Long-term testing is generally recommended every three months over the first year, every six months over the second year, and yearly afterwards, as appropriate. At least one additional batch should be added to the stability testing program annually.

(4) For those biotechnological/biological products and other APIs having shelf-lives of one-year or less, it is recommended that testing be conducted monthly for the first three months, and at three month intervals after that.

f. Tests should be conducted on each product form if the API is marketed in more than one product form (e.g., different grades). Testing each form would not be needed if there is sufficient data to show that product form does not affect stability.

(1) Product form should be stated on the label of the API.

g. Changes in a manufacturing site, materials or manufacturing process should be evaluated to determine if these changes affect stability.

(1) Data should be developed to show that such changes do not adversely affect stability. Samples from batches produced under the changes should be added to the stability testing program.

D. Special Testing

1. For each lot of API purporting to be pyrogen free or meeting specified endotoxin limits, appropriate laboratory tests should be conducted to determine conformance to such specification. Test procedures should be written and followed.

2. Appropriate laboratory controls should be implemented to assess changes in the manufacturing process that may affect the physical properties of an API.

3. Impurity profiles should be established and maintained for each API process, which identifies or quantifies each impurity, the range of each impurity observed, and the classification of each impurity. Test procedures for establishing impurity profiles should be written and followed.

    a. Impurities classifications may include the following:

        (1) Organic impurities (process and drug related). These may arise during the manufacturing process and/or storage. They may be identified or unidentified, volatile or nonvolatile, and include:

            (a) Starting materials
            (b) By-products
            (c) Intermediates
            (d) Degradation products
            (e) Reagents, ligands, and catalysts

        (2) Inorganic impurities. These may derive from the manufacturing process. They should normally be known and identified, and include:

            (a) Reagents, ligands and catalysts
            (b) Heavy metals
            (c) Inorganic salts
            (d) Other materials such as filter aids, and charcoal.

        (3) Residual solvents

E. Reserve Samples

1. Appropriately identified reserve samples should be retained that represent each lot of API and key intermediate.

2. The reserve sample should consist of at least twice the quantity necessary for all tests required to determine whether the API or key intermediate meets its established specifications.

3. The reserve sample should be retained for one year after the expiration or final reevaluation date of the lot.

    a. The reserve sample should be stored under conditions consistent with product labels, in the same packaging system in which the API or key intermediate is stored or in one that is equivalent to the marketed packaging system.

    b. Reserve samples should be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve samples. Any evidence of reserve sample deterioration should be investigated. The results of the examination should be recorded and maintained with other stability data on the API or key intermediate.

F. Laboratory Animals

1. Animals used in testing starting materials, reagents, intermediates, in-process materials, or APIs for compliance with established specifications should be maintained and controlled to ensure their suitability for their intended use. Animals should be identified, and adequate records should be maintained showing the history of their use.

X. **Records and Reports**

A. General Controls

1. Any production, control, or distribution record specifically associated with a batch of API should be retained for at least one year after the expiration date of the batch. For APIs with reevaluation dates, records should be retained for three years after the batch is completely distributed.

2. Records should be maintained for all components and API containers for at least one year after the expiration date of the batch. For APIs with reevaluation dates, records should be retained for three years after the batch is completely distributed.

3. All records or copies of such records, should be readily available for authorized inspection by the agency during the retention period at the establishment where the activities described in such records occurred. These records or copies of them should be subject to photocopying or other means of reproduction as part of such inspection. Records that can be promptly retrieved from another location by computer or other electronic means are acceptable.

4. Records may be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment should be readily available.

5. Written records should be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each API to detect the need for changes in specifications or manufacturing or control procedures. Written procedures should be established and followed for such evaluations and should include provisions for:

    a. A review of a representative number of batches, whether approved or rejected, and the records associated with the batch.

    b. A review of all complaints, recalls, returned or salvaged APIs, and subsequent investigations conducted.

6. Procedures should be established to ensure that the responsible officials of the firm, if they are not personally involved in, or immediately aware of, such actions, are notified in writing of any investigations conducted, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

B. Equipment Cleaning and Use Record

1. A written record should be maintained of major equipment cleaning and maintenance (except routine maintenance such as lubrication and adjustments), that shows the date, time, product, and lot number of each batch processed.

2. If equipment is dedicated to manufacturing one product, then individual equipment records are not necessary if lots or batches of such products follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use should be part of the batch record. The persons performing and checking the cleaning and maintenance should date/sign or initial the record showing that the work was done. Entries in the record should be in chronological order.

C. Component, API Container, Closure, and Labeling Records

1. These records should include the following:

   a. The identity and quantity of each shipment of each lot of components, API containers, closures, and labeling, the name of the supplier; the supplier's lot number(s) if known; the receiving code, and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, should be listed if known.

   b. The results of any test or examination performed and the conclusions derived from this.

   c. An inventory record of labeling and each component, and a reconciliation of the use of labeling and each lot of component. The inventory record should contain sufficient information to identify any batch or lot of API associated with the use of each component.

   d. Documentation of the examination and review of labeling and API containers for conformity with established specifications.

   e. The disposition of rejected components, API containers and labeling.

D. Master Production and Control Records

1. To ensure uniformity from batch to batch, master production and control records for intermediates and APIs, including each batch size thereof, should be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records should be described in a written procedure and such written procedure should be followed.

2. Master production and control records should include:

    a. The name (chemical nomenclature) of the intermediate or API and any standard to which it conforms (e.g., U.S.P.).

    b. A complete list of components designated by names or codes sufficiently specific to show any special quality characteristic;

    c. An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations in the amount of components necessary for the manufacture of the intermediate and API are acceptable provided they are justified in the master production and control records;

    d. A statement concerning any calculated excess of component;

    e. A statement of theoretical weight or measure at appropriate phases of processing;

    f. A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation is initiated;

    g. Description of the intermediate or API containers and specimens or copies of labeling to be used;

    h. Complete manufacturing and control instructions, any sampling to be performed, testing procedures, specifications, special notations and precautions to be followed.

E. Batch Production and Control Records

1. Batch production and control records should be prepared for each batch of intermediate and API and include complete information relating to the production and control of each batch. These records should include:

    a. An accurate reproduction of the appropriate master production and control record, checked for accuracy, dated and signed.

    b. Documentation that each significant step in the manufacture, control and packaging was accomplished including:

        (1) Dates;
        (2) Identity of individual major equipment;
        (3) Specific identification of each component or intermediate used;
        (4) Weights and measures of components used during manufacture;
        (5) In-process and laboratory control results;
        (6) A statement of the actual yield compared against a theoretical yield at appropriate phases of manufacture;
        (7) Description of intermediate and API containers;
        (8) Any sampling performed;
        (9) Signatures of the persons performing and directly supervising or checking each significant step in the operation;
        (10) Any investigations conducted under Section 10.6.
        (11) Results of release testing.

F. Production Record Review

1. Batch production and control records for APIs and intermediates should be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures and specifications before a batch is released or distributed.

2. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch to meet any of its specifications is thoroughly investigated, whether or not the batch has already been distributed. The investigation should extend to other batches

of the same intermediate or API and other batches that may have been associated with the specific failure or discrepancy. A written record of the investigation should be prepared that includes the conclusions and follows up.

3. Written procedures should be established and followed requiring the quality control unit to review and approve all API production, control, and laboratory records, including packaging and labeling, to determine compliance with all established and approved written procedures and specifications before a batch is released or distributed.

4. Written procedures should be established and followed requiring the thorough investigation of any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components or in-process materials to meet any of its specifications (including any out-of-specification test result), whether or not the batch has already been distributed. The investigation should extend to other batches of the same API and other APIs that may have been associated with the specific failure or discrepancy. Such procedures should include:

    a. Procedures to identify the cause of the failure or discrepancy;

    b. Criteria for assigning out-of-specification results to sampling or laboratory error;

    c. Scientifically sound and appropriate procedures and criteria for excluding any test data found invalid due to a laboratory or sampling error;

    d. Scientifically sound and appropriate criteria for additional sampling and testing, if necessary, during the investigation;

    e. Procedures and criteria for extending the investigation to other batches of intermediates or APIs;

    f. Procedures for the quality control unit's review and evaluation of the investigation, including all test results, to ensure a thorough investigation;

g. Criteria for approving or rejecting batches involved, and for taking action on other batches and products if suggested by the investigation.

5. A written record of the investigation should be prepared and should include:

a. The reason for the investigation;

b. A report summarizing the investigation conducted, including all laboratory tests;

c. The results of the investigation, including all laboratory test results involved in the investigation;

d. Scientifically sound and appropriate justification for excluding any out-of-specification laboratory result found invalid;

e. If laboratory results are found invalid, the subsequent laboratory results supporting the final determination of conformity to all appropriate specifications for acceptance;

f. The conclusions and subsequent actions concerning all batches of intermediates and APIs that may have been associated with the failure or discrepancy;

g. The signature(s) and date(s) of the person(s) responsible for approving the record of investigation;

h. The signature(s) and date(s) of the person(s) responsible for the final decision on disposition of the batch, and on other batches and products involved.

G. Laboratory Records

1. Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

a. A description of samples received for testing with identification of the source (i.e., location from where sample was obtained), quantity, lot number or other distinctive code, date sample was

taken, and dates the sample was received for testing.

(1) A description of any special storage conditions for test samples.

b. A statement of each method used in testing the sample. The statement should identify the data and/or source that documents the validity of sample test methods to meet proper standards of accuracy and reliability.

c. If the method employed is in the current revision of the United states Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,[3] or other recognized standard references, or detailed in a Drug Master File or approved new drug application and the referenced method is not modified, a statement showing the method and reference will suffice.

d. The suitability of all testing methods used should be verified under actual condition of use.

e. A statement of the weight or measure of the sample used for each test, where appropriate.

f. A complete record of all data secured during each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, intermediate, API, or in-process material and lot tested.

g. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

h. A statement of the test results and how they compare with established standards of identity, strength, quality, and purity for the component, intermediate, API, or in-process material tested.

[3] Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-3301.

i. The initials or signature of the person who performs each test and the date(s) the tests were performed.

j. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

2. Complete records should be maintained of any modification of an established analytical method. Such records should include the reason for the modification and data to verify that the modification produces results that are at least as accurate and reliable as the established method.

3. Complete records should be maintained of the preparation, testing and standardization of laboratory reference standards, reagents, and standard solutions.

4. Complete records should be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.

5. Complete records should be maintained of all stability testing performed.

H. Distribution Records

1. Distribution records should contain the name of the API or intermediate, as appropriate, the name and address of the consignee, carrier, date and quantity shipped, and lot or control number.

I. Complaint Files

1. Written procedures describing the handling of all written and oral complaints regarding an API or intermediate should be established and followed. Such procedures should include provisions for:

a. The quality control unit's review of any complaint involving the possible failure of an API or intermediate to meet any of its specifications and a determination as to the need for an investigation following the section on production record review.

b. Review to determine whether the complaint represents a serious

and unexpected event that would require notification to users of the API or intermediate.

2. A written record of each complaint should be maintained in a file designated for APIs or intermediates. The file should be maintained at the establishment where the API or intermediate was manufactured, processed, or packed, or such files may be maintained at another facility if the written records in such files are readily available for inspection at that other facility.

3. Written records involving an API should be maintained until at least one year after the expiration date of the API, or one year after the date that the complaint was received, whichever is longer. For APIs with reevaluation dates, such written records should be maintained for three years after the batch is distributed.

    a. The written record should include the name of the API, lot number, the name of the complainant, nature of complaint, and replies to the complainant.

    b. Where an investigation under the section on production record review is conducted, the written record should include the findings of the investigation and corrective actions taken. The record or copy of the record of the investigation should be maintained at the establishment where the investigation occurred following the section on records and reports.

    c. Where an investigation is not conducted, the written record should include the reason why an investigation was found unnecessary, and the name of the responsible person making such a determination.

XI. **Returned and Salvaged APIs and Intermediates**

A. Returned APIs and Intermediates

1. Returned APIs and intermediates should be identified as such and held. If the conditions under which returned APIs and intermediates have been held, stored, or shipped before or during their return, or if the condition of their containers, cartons, or labels, from storage or shipping, casts doubt on their safety, identity, strength, quality or purity, the returned API or intermediate

should be destroyed unless examination, testing, or other investigations prove the product meets appropriate standards of safety, identity, strength, quality, and purity.

2. An API or intermediate may be reprocessed, as discussed in the section on reprocessing and reworking provided the subsequent material meets appropriate standards, specifications, and characteristics. Records of returned APIs and intermediates should be maintained and should include their names and label potencies (if applicable), lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and their ultimate disposition. If the reason for the return implicates associated batches, an appropriate investigation should be conducted following the section on production record review. Procedures for the holding, testing, and reprocessing of returned APIs and intermediates should be in writing and followed.

B. API and Intermediate Salvaging

1. APIs and intermediates subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures should be neither salvaged, used in further manufacturing, nor returned to the marketplace. Whenever there are doubts that APIs and intermediates have been subjected to such conditions, salvaging operations may be conducted only if there is: (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the APIs and intermediates meet all applicable standards of identity, strength, quality, and purity; and, (b) evidence from inspection of the premises that the APIs and intermediates and their associated packaging were not subjected to improper storage conditions from the disaster or accident. Records including name, lot number, and disposition should be maintained for APIs and intermediates covered by this section.

XII. **Validation**

A. Process Validation

1. Manufacturers should be actively engaged in a validation program for all distributed APIs.

2. Validation should extend to those steps determined to be critical to the quality and purity of the final API, and should include:

    a. Definition of the API in terms of its critical product attributes. Attributes to be considered should include chemical purity, qualitative and quantitative impurity profiles, physical characteristics such as particle size, bulk/tap density, polymorphic forms, moisture and solvent content, homogeneity, and microbial quality (if the product is susceptible to microbial contamination).

    b. Identification of process parameters that may affect the critical quality attributes of the API. Critical parameters should be determined by scientific judgement, and should typically be based on knowledge derived from research, scale-up batches, or manufacturing experiences with similar products.

    c. Determination of both the extended range for each critical process parameter and the normal (target) operating range expected to be used during routine manufacturing and process control. Data to substantiate the ranges for critical process parameters should generally be obtained from research or pilot scale batches, unless a specific parameter can only be evaluated on a production scale.

3. Examples of processing steps that may be critical include:

    (1) Phase changes, such as dissolution or crystallization,

    (2) Phase separation, such as filtration or centrifugation,

    (3) Steps that cause chemical changes, such as the addition or removal of water.

    (4) Steps that alter temperature or pH.

    (5) Mixing of multiple components; and ,

    (6) Steps that cause changes in surface area, particle size, bulk/tap density or homogeneity.

4. Parameters to control and monitor for critical process steps may include, but

are not limited to reaction times, reaction temperatures, reactant ratios, concentrations, pressures, pH, and yields.

5. Establishing impurity profiles is an important aspect of process validation. Impurities profiles should be established for each API. In principle, process validation should provide conclusive evidence that the levels of contaminants are reduced as processing proceeds from early intermediate steps to final synthesis and purification steps.

B. The Validation Protocol

1. A written validation protocol should be established that specifies how process validation will be conducted. The protocol should identify who is responsible for design, review, approval, and documentation of each validation phase.

2. The validation protocol identifies the process, equipment used, stages at which various substances are added, critical steps in the process, extended ranges for critical process parameters, operating (target) ranges during routine production, and monitoring points.

3. The protocol should specify a sufficient number of process runs to prove consistency of the process, and provide an accurate measure of variability among successive runs. The number of batches should depend on the extent of validation and complexity of the process or importance of any process change under consideration.

4. The protocol should also address the quality of materials used in the process (e.g., starting materials, intermediates, recycle streams, new and recovered solvents, water, catalysts, gases, and other process aids) and evidence of the performance and reliability of equipment and systems. Execution of the protocol and the test results should be documented.

C. Prospective Validation

1. Prospective validation is necessary for new production processes, and is the preferred method of establishing confidence in any process.

2. Validation is an activity that should span the life of a new API process. Data from research and pilot scale batches should identify critical product attributes and specifications, critical steps, control ranges, and in-process tests. Scale-up batches should generate data to confirm or refine earlier work, and production scale batches should provide data showing consistency of the process.

3. Prospective validation should involve obtaining and evaluating documented processing and analytical control information for multiple batches manufactured, sampled, and tested according to a preestablished validation plan.

4. Fully validated analytical methods capable of quantifying the product quality attributes should be available and used during process validation. Resulting data should be evaluated by the appropriate personnel. A validation report that justifies the conclusions should be prepared and approved by the quality control unit.

D. Retrospective Validation

1. Retrospective validation is acceptable for a process that had not been validated, but has been used for an extended period without significant changes in raw materials, equipment, systems, facilities, or in the production process that would affect the critical quality attributes of the API.

2. Retrospective validation is acceptable only if:

    a. Critical product attributes and critical process steps have been identified and documented.

    b. Appropriate in-process specifications and controls have been established and documented.

    c. There have been no process/product failures attributable to other than operator error or equipment failure unrelated to equipment suitability.

    d. Impurity profiles have been established for the existing API.

    e. In-process and end-product test data show lot to lot consistency.

3. Retrospective validation should involve reviewing and analyzing physical and analytical controls utilized for past batches and extending from starting materials to the finished API.

4. Retrospective validation should include a written validation protocol prior to execution, which identifies the batches and the data that will be evaluated to determine the consistency of the process.

5. Retrospective validation should include examining a sufficient number of batches to demonstrate process consistency.

6. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications.

7. All batches selected for review should have been manufactured by essentially the same process (including the same range of operating conditions, the same equipment and in-process and materials specifications) and have a documented history of controls and test results evaluated against current controls and product specifications.

8. Additional testing of retained samples and/or the production of new batches may be needed to obtain the necessary amount or type of data to sufficiently validate the process.

9. The data obtained should be evaluated, as with prospective validation, by the appropriate personnel, and a final validation report should be approved by the quality control unit.

XIII. **Changes to a Validated Process**

A. Change Control System

1. To ensure a continued state of process control, a formal change control system should be established that is designed to evaluate all changes that may affect the production and control of the API or intermediate. Written procedures should provide for the identification, documentation, appropriate review, and approval of both anticipated and unanticipated changes in components, facilities, support systems, equipment (including computer

hardware), processing steps, and packaging materials, and computer software. Any changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality control unit.

2. Before carrying out changes to a validated process, the change control system should provide for identification of all changes (e.g., maintenance, supplier, and production), an assessment of likely effects on the process, and formal approval by the quality control unit to continue with the change. In addition, written procedures should clearly identify how the changes will be implemented, monitored, and justified. Written procedures should also provide for current dosage form manufacturers to be notified of changes from established production and process control procedures that are identified in relevant drug master files.

3. Change-control procedures should include the following:

    a. Periodic evaluations of production processes to detect potential problems.

    b. Evaluation of all changes being contemplated.

    c. Evaluation of all changes to determine if and to what extent revalidation is needed.

    d. Evaluation of changes to assess their potential effects on other API processes.

    e. Determination if the changes will require additional stability studies on the API.

    f. Determination if additional testing is needed for impurity profiles, polymorphism, or other physical attributes.

B. Change Control Classification

1. The change-control program may provide for a classification scheme to evaluate changes in components, manufacturing sites, scale of manufacturing, manufacturing equipment, and production processes. This classification procedure can help in determining what level of testing, validation, and documentation is needed to justify changes to a validated

process. For example, changes may be categorized as minor, moderate, or major, or by categories (e.g., Levels 1 - 3) depending on the nature and extent of the changes, and the effects these changes may impart on the process. In all cases, scientific judgement should determine what additional testing and validation studies are needed to justify a change in a validated process.

2. Using the classification schemes described above as examples, a minor (Level I) change could be defined as one that is unlikely to have a detectable impact on the critical attributes of the API. Such changes would not shift the process in any discernible manner, and may be implemented with minimal testing and validation. For example, "like-for-like" equipment replacements where equipment is repaired to its initial validation state or in which identical or similar equipment is introduced into the process, would be unlikely to affect the process if adequately installed and qualified.

3. A moderate (Level 2) change could have a significant impact on the critical quality attributes of the API. For example, solvent changes in early processing steps could be justified by generating analytical data to show that the intermediate produced after the solvent change is equivalent in quality and purity to the intermediate produced before the change.

4. A major (Level 3) change would be likely to have a significant impact on the critical quality attributes of the API. For example, a change in solvent used for the final crystallization could have a significant impact on the impurity profile, physical attributes, and other critical attributes of the API. Such changes would warrant major testing and suitable revalidation studies to justify the changes.

XIV. **Reprocessing/Reworking of Intermediates and APIs**

A. Reprocessing by Repeating a Chemical Reaction

1. Reprocessing an intermediate or API by repeating a chemical reaction may not be feasible in most cases since this may produce new impurities of unknown toxicity. The uncertainty and risks associated with this type of reprocessing may not warrant such action, and it is probably best to dispose of the affected product rather than subject it to a second chemical reaction.

2. Where such reprocessing occurs, written procedures should be established

and approved by the quality control unit that clearly specify the conditions and limitations of repeating chemical reactions. In addition, the procedures should establish how reprocessing will be validated, and what additional tests will be conducted on the reprocessed material to show that the resulting material is of a strength, quality, and purity comparable to that normally produced by the process. These tests may include at a minimum, assays for potency, complete impurity profiles, stability testing, and physical attributes testing.

B. Reprocessing by Physical Manipulations

1. Intermediates and API batches that occasionally do not conform to specifications for percent transmittance/color, potency, impurities, or other critical product attributes may be reprocessed by repeating a crystallization step or other physical manipulation step (e.g., dissolution, filtration, milling) that is part of a validated process.

2. Reprocessing by physical manipulation to improve purity or physical properties of intermediates and APIs would be justified if:

    a. A thorough investigation is conducted and documented to determine the cause of the non-conformance, and appropriate corrective action is taken to preclude a recurrence. For example, if investigation of the non-conformance and/or review of the process reveals an abnormal recrystallization rate, it would be reasonable to identify the cause of the process variability, and incorporate the recrystallization as part of the normal process.

    b. The reason for non-conformance of the batch or material is evaluated to determine its suitability for reprocessing. For example, a batch not conforming with a visual color test may be further purified by recrystallization, but a batch with high impurity levels may not be an ideal candidate for reprocessing if it requires several recrystallizations to bring the batch into specifications.

    c. All reprocessing procedures should be reviewed and approved by the quality control unit. These procedures should clearly specify the conditions and limitations for reprocessing by physical manipulations. For example, one or more recrystallizations from the final solvent may be justified, but continuous reprocessing of batches until they meet a given quality specification is

unacceptable.

d. A specific batch production record should be generated to cover the reprocessing step(s) and subsequent handling.

e. Appropriate tests should be conducted on the reprocessed material to ensure that reprocessing does not adversely affect the identity, strength, quality, or purity of the intermediate or API. These tests should include at a minimum, assays for potency, physical attributes, and impurity profiles. In all cases, the significance of the non-conformance and its impact on the critical quality attributes of the intermediate or API would determine how much analytical data is sufficient to justify the reprocessing.

f. Reprocessing operations should be subjected to appropriate validation to show that these steps consistently perform the expected functions and result in batches that comply with all established standards, specifications, and characteristics. Validation should provide for comparing the impurity profiles of reprocessed batches against batches manufactured by the validated process.

C. Reworking of Intermediates and APIs

1. Reworking batches that do not conform to established standards or specifications, by using processing steps that are different from the validated process should entail extensive investigation, evaluation, and documentation to show that the reworked product is of equivalent quality to that produced by the original process.

2. Validation of reworking procedures is critical and should clearly show that reworking does not adversely affect the identity, strength, quality, or purity of the intermediate or API.

3. Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the validated process.

4. Often, the reworked material may necessitate examination by sensitive analytical procedures, such as those used for qualifying reference standards.

5. Because reworking involves changes to validated processes, the changes

should be addressed and handled through process change control procedures.

XV. Contamination

A. Control of Chemical and Physical Contaminants

1. Written procedures should be implemented to prevent objectionable chemical and physical contamination, including cross-contamination in APIs and intermediates.

2. Dedicated production, which may include facilities, air handling equipment and/or process equipment, should be employed where both of the following conditions exist:

    a. Contaminants pose a special danger to human and animal health; such contaminants include, but are not limited to, penicillin, cephalosporins, cytotoxics, and infectious agents;

    b. There are no reasonable methods for cleaning and removing contaminant residues from buildings, facilities and equipment.

3. If a reasonable possibility exists that an API or intermediate has been exposed to cross-contamination, the substance should be tested for the presence of the potential contaminant, and appropriate limits should be established for such contaminants. APIs and intermediates that exceed the established limits should not be used for further manufacture.

XVI. References:

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5. FDA Biotechnology Inspection Guide, Office of Regional Operations, November 1991

6. FDA Guideline to Inspection of Validation of Cleaning Processes, Office of Regulatory Affairs, July 1993

7. HHS/FDA "International Conference on Harmonisation; Stability Testing of New Drug Substances and Products; Guideline; Availability; Notice," Federal Register, September 22, 1994

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11. "Problems in Bulk Pharmaceutical Chemical Production: An FDA Investigator's View," Dale E. Cooper, Pharmaceutical Technology, June 1984, Pages 72 - 80

12. "BPC's and cGmp's," Anthony G. Lord, Pharmaceutical Engineering, May/June 1988, Vol. 8, N. 3, Pages 30 - 35

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and Validation," Edwin Rivera Martinez, Pharmaceutical Engineering, May/June 1994, Volume 14, Number 3, Pages 8 - 14

B. Industry Documents:

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4. "FDA Regulation of Bulk Pharmaceutical Chemicals -- An Industrial Commentary: Part I," F. Demmer, et al, Pharmaceutical Technology, October 1994, Pages 80 - 90

5. "FDA Regulation of Bulk Pharmaceutical Chemicals -- An Industrial Commentary: Part II," F. Demmer, et al, Pharmaceutical Technology, December 1994, Pages 36 - 43

6. Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, The International Pharmaceutical Excipients Council, July 1995

7. "PhRMA Guidelines for the Production, Packing, Repacking or Holding of Drug Substances," QC Bulk Pharmaceuticals Work Group, Quality Steering Committee, PhRMA Science and Regulatory Section, Part I and Part II, Pharmaceutical Technology, December 1995 and January 1996

C. Other Documents:

1. Guidelines for the Manufacture of Active Pharmaceutical Ingredients (Bulk Drug Substances), Pharmaceutical Inspection Convention, PH 2/87, June 6, 1987

2. "FDA's Guideline for Bulk Pharmaceutical Chemicals - A Consultant's Interpretation," Robert E. Moore, Pharmaceutical Technology, September

1992, Pages 88 - 100

3. EFPIA/CEFIC Final Draft Good Manufacturing Practices for Active Ingredient Manufacturers, Bulk European Federation of Pharmaceutical Industries Association/European Chemistry Industry Council, December 1995

4. Commercial Executive Order for the Manufactures of Active Ingredients for Drugs, Federal Ministry of Health, Republic of Germany, October 26, 1994

5. "Good Manufacturing Practices for Active Pharmaceutical Ingredients (Bulk Drug Substances) in WHO Expert Committee on Specifications for Pharmaceutical Preparations, 32nd Report," Geneva 1992, ISBN 92 4 1208236

6. Good Manufacturing Practices for Pharmaceutical Products, Annex - Guidelines on the Validation of Manufacturing Processes, WHO/Pharm/93.562/Rev. 2

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